

Amendments to the Specification:

Please replace the following paragraphs with the revised versions provided herein below:

On page 1, beginning at line 2 through line 7, under the heading Related Applications, please amend as follows:

This application claims benefit of the United States Provisional Application Number 60/269,198, filed February 15, 2001, the disclosure of which is incorporated herein by reference in its entirety. This application further claims the benefit of United States Provisional Application entitled "Insulinization of the Liver", filed January 11, 2002, Application Serial No. ~~not yet assigned~~ 60/347,713, the disclosure of which is incorporated herein by reference in its entirety.

On page 32, beginning at line 17 through line 28, please amend as follows:

According to these embodiments of the present invention, the insulin polypeptide is preferably insulin or an insulin analog. More preferably, the insulin polypeptide is human insulin or a human insulin analog, and, still more preferably, the insulin polypeptide is human insulin. When the insulin polypeptide in the structure of Formula V is human insulin and the oligomer is conjugated to the B29 lysine of the human insulin, this insulin-oligomer conjugate is referred to herein as HIM2. HIM2 is a polydispersed mixture of insulin-oligomer conjugates. It may be still more preferable to use a substantially monodispersed or monodispersed mixture of insulin-oligomer conjugates as described in U.S. Patent No. 6,828,297 issued December 7, 2004, Application Serial No. 09/873 filed June 4, 2001 by to Ekwuribe et al. entitled "Mixtures of Insulin Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same". This insulin polypeptide-oligomer conjugate of Formula V is amphiphilically balanced when the insulin polypeptide is insulin.

Bridging pages 32 and 33, beginning at line 29 on page 32 through line 22 on page 33, please amend as follows:

HIM2 may be synthesized by various methods as will be understood by those skilled in the art. HIM2 is preferably synthesized utilizing proinsulin as a starting material as described in U.S. Patent Application Serial No. 10/036,744 filed December 21, 2001 No. 6,913,903 issued July 5, 2005, by to Soltero et al. entitled "Methods of Synthesizing Insulin Polypeptide-Oligomer Conjugates, and Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same". For example, HIM2 has been synthesized as follows. Recombinant proinsulin having a leader peptide (MW 10,642 Daltons) was obtained from Biobras, of Belo Horizonte, Brazil. A 2.32×10^{-3} mmol portion of the proinsulin was

dissolved in 10 mL of DMSO. To the solution was added 324 μL of triethylamine. The resulting solution was allowed to stir for 5 minutes, and then a solution of activated methylheptaethylene glycol ((PEG7)-hexyl oligomer) (9.30×10^{-3} mmol) in acetonitrile was added. The course of the conjugation (acylation) reaction was monitored by HPLC. When reaction appeared to be complete, it was quenched by addition of 3.54 mL of 5% aqueous trifluoroacetic acid solution. The reaction mixture was then processed and exchanged into 100 mM Tris-HCl Buffer, pH 7.6 to provide a product mixture. An aliquot of the Tris-HCl solution of the product mixture was analyzed by HPLC to determine the polypeptide concentration. A solution of trypsin (TPCK treated; from bovine pancreas) was prepared in 100 mM Tris-HCl Buffer, pH 7.6. A solution of carboxypeptidase B (from porcine pancreas) was prepared in 100 mM Tris-HCl Buffer, pH 7.6. The product mixture ($0.424 \mu\text{mol/mL}$) was then allowed to react with trypsin ($5.97 \times 10^{-4} \mu\text{mol/mL}$) and carboxypeptidase B ($1.93 \times 10^{-4} \mu\text{mol/mL}$). After 30 minutes, the reaction was quenched by the addition of 1.58 mL of 1% trifluoroacetic acid in acetonitrile. The major products were identified by HPLC retention time (relative to the retention times of known reference standards) and mass spectral analysis. Insulin (10%) and Lys^{B29}-Hexyl-PEG7-Oligomer-Conjugated Insulin (84%) were thus obtained.

Bridging pages 34 and 3, beginning at line 29 on page 33 through line 19 on page 34, please amend as follows:

The insulin polypeptide-oligomer conjugates employed in the various embodiments described above may be synthesized by various methods as will be understood by those skilled in the art. For example, polydispersed insulin polypeptide-oligomer conjugates may be synthesized by the methods provided in one or more of the following references: U.S. Patent No. 5,359,030 to Ekwuribe; U.S. Patent No. 5,438,040 to Ekwuribe; U.S. Patent No. 5,681,811 to Ekwuribe; U.S. Patent No. 6,309,633 to Ekwuribe et al.; and U.S. Patent Application Serial No. 10/036,744 filed December 21, 2001 No. 6,913,903 issued July 5, 2005, by to Soltero et al. entitled "~~Methods of Synthesizing Insulin Polypeptide-Oligomer Conjugates, and Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same~~", the disclosures of which are incorporated herein by reference in their entireties. Non-polydispersed (e.g., substantially monodispersed and monodispersed) insulin polypeptide-oligomer conjugates may be synthesized by methods provided in one or more of the following references: U.S. Patent Application Serial No. 09/873,797 filed June 4, 2001 No. 6,858,850 issued February 22, 2005, by to Ekwuribe et al. entitled "~~Mixtures of Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same~~"; U.S. Patent Application Serial No. 09/873,899 filed June 4, 2001 No. 6,828,297 issued December 7, 2004 by to Ekwuribe et al. entitled "~~Mixtures of Insulin Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same~~"; U.S. Patent Application Serial No. 10/036,744 filed December 21, 2001 No. 6,913,903 issued July 5,

2005, by to Soltero et al. entitled "~~Methods of Synthesizing Insulin Polypeptide Oligomer Conjugates, and Proinsulin Polypeptide Oligomer Conjugates and Methods of Synthesizing Same~~", the disclosures of which are incorporated herein by reference in their entireties. Oligomers according to embodiments of the present invention are preferably substantially monodispersed and are more preferably monodispersed.